REMARKS

Applicants hereby request reconsideration and withdrawal of the rejections and objections set forth in the Office Action of December 29, 2005, in view of the foregoing amendments and following remarks.

The Claim Amendments and Pending Claims

Independent claims 1 and 30 (as well as currently withdrawn independent claim 17) are amended to read on humanized antibodies (and fragments thereof) that (1) immunoreacts with an epitope on tissue factor ("TF") that comprises Trp45 and (2) inhibits binding of factor VIIa to TF. The originally filed specification and claims provide ample support for this amendment. See, e.g., paragraphs 0063 and 0090 of the published version of the application - i.e., US Patent Publication No. 20050106139. Therefore, the amendment adds no new matter. Applicants have also adopted the Examiner's suggestion and amended the claims such that they recite "fragments" as well as "antibodies." As acknowledged by the Office Action, antibody "fragments" are implicit in the definition of antibodies provided in the specification. Accordingly, this amendment also adds no new matter. Applicants have hereby cancelled several claims, without prejudice, to focus the issues for prosecution in the instant application.

Claims 1, 4-7, 11, 15, 17, and 30-32 are pending. Claim 17 is currently considered withdrawn (all other claims are at issue), but remains pending in the event that rejoinder becomes proper. Claims 1 and 30 are the only independent claims that are pending and presently at issue.

The Amended Claims and Specification are in Proper Form

The Office Action objected to claims 1 and 4-7, as previously presented, because the claims recited "antibodies," while dependent claims are directed to antibody "fragments." The Office Action acknowledged that the specification defines antibodies as generally including fragments of "full length" antibody molecules (such that the claims were in proper form). Nonetheless, in accordance with the Examiner's suggestion, Applicants hereby amend the independent claims to

explicitly recite antibodies *and* fragments thereof, to promote clarity and overcoming any basis for objection.

The Office Action also objected to the lack of disclosure of the sequence of human tissue factor. Accepting the Examiner's suggestion, Applicants hereby add the sequence for mature human TF (as SEQ ID NO:14), which is set forth in, e.g., US Patent 5,223,427, which patent the subject patent application incorporates by reference (see, e.g., paragraphs 0007 and 0228 of the published application). As such, the amendment adds no new matter. Applicants will submit an amended sequence listing in due course.

The Office Action's Definiteness Rejections are Now Moot

The Office Action rejected claims 12, 13, 16, and 13 under 35 USC § 112, second paragraph, as allegedly indefinite. While not conceding that this rejection was correct, Applicants note that these claims have been cancelled, thereby obviating these rejections.

The Enablement Rejections also are Now Moot

The Office Action also rejected claims 1 and 8-10 under 35 USC § 112, first paragraph, for allegedly failing to comply with the enablement requirement. Specifically, the Office Action objected to claims to antibodies having binding affinities of 10^{-10} to 10^{-15} M. While not conceding anything concerning this rejection, Applicants note that they have hereby cancelled claims 8-10. As such, there no longer is any basis remaining for rejecting the pending claims (e.g., claim 1) in respect of the arguments set forth in the Office Action.

The Amended Claims are Novel

The Office Action rejected claims 1-4, 6-9, 11, 12, 15, 16, and 30-33 under 35 USC § 102(b) as allegedly lacking novelty over US Patent 5986065 (Wong et al. - hereinafter referred to as "the Wong patent"). The Office Action alleged the Wong

patent discloses antibodies that bind TF and inhibit the binding of FVIIa to TF (citing specifically the abstract and Figure 4). Applicants respectfully disagree.

The abstract of the Wong patent states, "Antibodies of the invention can bind native TF, either alone *or present in a TF:VIIa complex*, effectively preventing *factor X binding* to TF *or that complex*..." Thus, contrary to the Office Action's position, the Wong patent *does not* disclose antibodies that inhibit TF:FVIIa binding. To the contrary, the Wong patent is, at its most relevant, neutral as to whether the antibodies bind TF alone *or only in complex* with FVIIa, so long as they block *Factor X* (i.e., not Factor VII) binding (see also, col. 2, lines 58-65). More importantly, preferred antibodies of the Wong patent "*do not* significantly inhibit the interaction between TF and factor VIIa, or inhibit activity of a TF:factor VIIa complex" (see col. 2, line 66 - col. 3, line 3) (emphasis added). Figures 3 and 4 reflect this inhibition of Factor X binding, rather than Factor VII binding (see, e.g., col. 17, lines 24-31). The subject matter of the current and previously pending claims is directed to humanized antibodies, and related compositions (e.g., cells expressing antibodies), that inhibit binding of TF to factor VIIa (FVIIa). This element is clearly lacking in the teachings of the Wong patent. Applicants respectfully submit that for this reason alone, the Wong patent fails to anticipate the current claims (Applicants further note that none of the other limitations of the current claims, e.g., an antibody that binds to an epitope comprising Trp45 of TF, are in any way taught or suggested by the Wong patent).

The Office Action further rejected claims 1-4, 6-9, 11-16, and 30-33 under Section 102(b) as allegedly lacking novelty over US Patent 6703494 (Kirchhofer et al. - hereinafter referred to as "the Kirchhofer patent"). The Kirchhofer patent discloses three antibodies that apparently inhibit formation of a TF:FVII complex: 7G11, 6B4, and HTF1. As noted in the Office Action, Kirchhofer et al. experimentally identified the key amino acid residues comprised in the epitopes on TF for these antibodies. Specifically, the epitope for 7G11 includes residues K46, S47, K48, F50, Y51, and T52; the epitope for 6B4 includes residues Y10, F76, Y94, E99, L104, and E105; and the epitope for HTF1 includes residues F76, Y94, E99 (though Kirchhofer

et al. speculate that the epitopes for HTF1 and 6B4 may be identical). None of these epitopes includes Trp45, which is required by the currently amended independent claims. As such, and as acknowledged by the Office Action, these epitopes "are not the same." For this reason, the Kirchhofer patent does not anticipate any of the pending claims under Section 102(b) (see, e.g., MPEP §2131).

The Amended Claims are Directed to Non-Obvious Subject Matter

The Office Action rejected claims 1 and 5 as allegedly encompassing subject matter that would have been obvious to a person having ordinary skill in the art given the disclosure of the Wong patent in view of US Patent 5081230 (Carney).

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the cited references (see, e.g., MPEP §2143.03).

The shortcomings of the Wong patent, in respect of teaching or suggesting elements of the presently claimed aspects of the invention are discussed above. The Office Action cited the Carney patent for its alleged teaching of methods for making antibody fragments, and not in respect of the elements of the independent claims. As such, the Carney patent does not compensate for the failing of the Wong patent to teach or suggest all of the elements of the claims and, accordingly, maintenance of a Section 103 rejection based on this combination of references would be misplaced.

The Office Action also rejected claims 1 and 5 under Section 103 as allegedly encompassing subject matter that would have been obvious to one given the disclosure of the Kirchhofer patent in view of the Carney patent. Applicants respectfully disagree.

The amended claims are directed to antibodies (or related compositions) that bind to an epitope on TF that comprises residue Trp45 and that inhibits TF:FVIIa binding. There is no suggestion or teaching in the Kirchhofer patent of an anti-TF antibody having these characteristics. In this respect, Applicants submit herewith the **Declaration of ...**, which includes a model comparing the spatial position of Trp45 with the epitopes of the allegedly FVIIa:TF complex-inhibiting antibodies disclosed in the Kirchhofer patent. The structure of TF, reflected in this model, demonstrates that one

of ordinary skill in the art would expect that the antibodies of the Kirchhofer patent would have epitopes that are distinct from an antibody that binds an epitope that comprises Trp45. As such, Applicants respectfully submit that the present claim amendments have overcome this basis for rejecting the claims under Section 103.

The Office Action further rejected claims 1-4, 6-9, 11-16, and 30-33 under Section 103 as allegedly encompassing subject matter that would have been obvious to a person having ordinary skill in the art given the disclosure of US Patent 5223427 (Edington et al.) in view of US Patent 5693762 (Queen et al.). Applicants respectfully submit that any basis for this rejection has been overcome by the present claim amendments, which limit the claims to humanized antibodies that bind to an epitope on TF that comprises Trp45 and inhibits TF:FVIIa complex formation.

The Edington patent discloses murine antibodies that allegedly block TF:FVII complex formation as well as polypeptides that inhibit the binding of such antibodies to TF. In one aspect, the Edington patent discloses anti-TF antibodies that immunoreacts with a polypeptide comprising TF residues 26-49. The Edington patent indicates that this polypeptide can block binding of anti-TF to TF, as well as polypeptides comprising residues 24-35, 144-159, 146-167, and 157-169.1 More specifically, in this respect, the Edington patent states:

> Thus, polypeptides p24-35 and p159-169 represent huTFh polypeptide binding-site analogs of the present invention. It should also be noted that the results obtained with p24-35, when taken in view of the similar results obtained with polypeptide p25-49, indicate that a huTFh-factor VII/VIIa binding site can be formed by the amino acid residue sequence those two polypeptides have in common, i.e., residues 30-35 as shown in FIG. 1 (--VNQVYT--).

Another passage of the Edington patent similarly focuses on more particular regions of TF, comprised in residues 25-49, that would exclude Trp45 (i.e., residues 30-

1 The Edington patent also identifies polypeptides comprising residues 40-71 and 41-49 as having the ability to block anti-TF binding (see Table 2), but does not identify such polypeptides as blocking the ability to bind factor VII/VIIa with the effect of inhibiting activation of factor X.

40, more particularly 30-35), in preferred binding sites for anti-TF antibodies (see col. 16, line 58 - col. 17, line 7).

In view of these facts, Applicants respectfully submit the Edington patent discloses antibodies that preferably bind to certain *regions* of TF, rather than epitopes. Furthermore, although linearly proximate, these *regions* encompass a number of spatially distinct regions of TF (a fact evidenced by the Declaration submitted herewith as well as the Kirchhofer patent). Perhaps more importantly, the Edington patent would point one of ordinary skill in the art to focus on residues 30-35, rather than other portions of residues 25-49, such as Trp45, in seeking to develop antibodies that block TF:FVII binding. In other words, there is no disclosure of a TF:FVII complex-inhibiting antibody comprising Trp45 as an epitope, nor is there any pointer to such an antibody in the Edington patent. There is only, at best, an invitation to try other residues in 25-49 (and even then, only after trying residues 30-35 and 36-40).

Additionally, as noted from the discussion of the Kirchhofer patent, above, one of ordinary skill would not expect that antibody that is specific for an epitope comprising, e.g., Lys46 of TF, which also is contained in the region identified by the Edington patent, would share the same epitope as an antibody that is specific for an epitope comprising Trp45. The ordinary artisan would reject such a view of anti-TF antibodies, given the spatial configuration of the molecule.

The Queen patent is only cited for its disclosure of humanized antibodies, which the Office Action acknowledges are not disclosed by the Edington patent. The Queen patent does not in any way compensate for the failure of the Edington patent to teach or disclose a TF:FVIIa complex-inhibitory antibody that is directed to an epitope comprising Trp45. As such, Applicants respectfully submit that the amended claims are patentable over the combination of the Edington and Queen patents.

Given these facts, Applicants respectfully submit that the claims are free of the cited prior art.

Conclusion

In view of the above, it is respectfully submitted that the application is now in condition for allowance and issue. Early action to that end is respectfully requested. The Commissioner is hereby authorized to charge any fees in connection with this application and to credit any overpayments to Deposit Account No. 14-1447. The Examiner is invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

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